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<p>(54) Title: TREATMENT OF INFLAMMATORY BOWEL DISEASE USING ORAL DOSAGE FORMS OF OMEGA-3 POLYUNSATURATED ACIDS</p>		
<p>(57) Abstract</p> <p>Inflammatory bowel disease, especially Crohn's disease and ulcerative colitis, is treated by administration of an oral dosage form, containing as an active principle an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof, which releases the acid in the ileum. Preferably the oral dosage form is a gelatine capsule coated with a poly(ethylacrylate-methyl-methacrylate).</p>		

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TREATMENT OF INFLAMMATORY BOWEL DISEASE USING
ORAL DOSAGE FORMS OF OMEGA-3 POLYUNSATURATED ACIDS

5 The present invention relates to the oral
administration of omega-3 polyunsaturated acids especially,
but not exclusively, eicosapenta-5,8,11,14,17-enoic acid
("EPA") and/or docosahexa-4,7,10,13,16,19-enoic acid
("DHA"). In particular, it provides enteric dosage forms
10 of omega-3 polyunsaturated acids for the treatment of
inflammatory bowel disease especially, but not exclusively,
Crohn's disease and ulcerative colitis.

15 It is known that DHA, EPA and other omega-3 poly-
unsaturated acids are of use in the treatment of
inflammatory bowel disease (see, for example, EP-A-0244832,
EP-A-0289204, EP-A-0311091 & WO-A-93/21912).

20 EP-A-0244832 discloses pharmaceutical compositions
containing certain unsaturated fatty acids with certain
specified stimulators. The compositions are of use for
treating disorders associated with prostaglandin
deficiency, especially gastrointestinal ulcers. The
unsaturated fatty acids are those which have 3 to 5
25 isolated double bonds and 18 to 22 carbon atoms arranged in
a straight chain and are capable of being methylated or
ethylated at one or two carbon atoms in positions 2, 3, 4,
16, 17, 18, 19 or 20. EPA is amongst the exemplified
acids. Reference is made to pH dependent delayed release
30 formulations containing polystyrene or polyacrylic
derivatives and to enteric coated products.

35 EP-A-0289204 discloses disinfectant and pharmaceutical
compositions comprising the lithium salt of a C_{13} - C_{22}
polyunsaturated fatty acid. Specified polyunsaturated
fatty acids include DHA and EPA. The pharmaceutical

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compositions can be for enteral, parenteral and topical administration and are for use in the treatment of conditions responsive to lithium and/or polyunsaturated fatty acid therapy. Specified conditions responsive to polyunsaturated fatty acid therapy include Crohn's disease and ulcerative colitis. Reference is made to providing an enteric coat of, for example, an acrylate or cellulose acetate phthalate to delay release of the salt until the intestine.

10

EP-A-0311091 discloses physiologically acceptable isotonic fat emulsions containing an omega-3-fatty acid or ester, a medium-chain length triglyceride, and an emulsifier. The fatty acid or ester component can be present as a pure compound or in the form of a fish oil and preferably is EPA. The emulsion is administered parenterally for, inter alia, treatment of chronic inflammatory bowel disease.

15

WO-A-93/21912 discloses the use of emulsions containing a polyunsaturated long-chain omega-3-fatty acid or ester for parenterally administration to treat inflammatory disorders including inflammatory bowel disease. The fatty acid or ester can be present as fish oil and preferred fatty acids include DHA and EPA.

25

Enteric coated products containing DHA or EPA have been reported for use in the treatment of other conditions (see EP-A-0336662, GB-A-2090529, JP-A-62201823, & WO-A-90/04391)

30

EP-A-0336662 discloses the microencapsulation of fish oil acids within an enteric coating to provide a stable, odorless and tasteless composition for incorporation into a food product to reduce plasma triglyceride, low density lipoprotein and cholesterol levels. The specified coating

35

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materials are ethyl cellulose, cellulose acetate phthalate and cellulose acetate trimelitate. Reference is made to release of the active below the pylorus in the upper portion of the intestine but there is no specific reference to targeting release to the ileum.

GB-A-2090529 discloses the prophylaxis and treatment of thrombosis using DHA or esters or amides thereof. Reference is made in general terms to intestine soluble coated tablets and to film coated tablets.

JP-A-62201823 discloses enterically coated capsules for treating enteral abnormal fermentation or diarrhoea which contain bacteria in an oil. The oil can be EPA and a number of enteric materials are specified including shellac, carboxymethyl cellulose, cellulose acetate phthalate, hydroxymethyl propylcellulose phthalate, and polyvinyl alcohol phthalate.

WO-A-90/04391 (and corresponding GB-A-2223943) discloses that enteric dosage forms of EPA, DHA and other omega-3 polyunsaturated fatty acids overcome the problem of belching and flatulence associated with oral administration of these acids. The exemplified coating is cellulose acetate phthalate/ethyl phthalate but reference is made to the use of polymethacrylate as the coating material.

Belluzzi et al (Dig. Dis. Sci. 39 (1994) 2589-2594) reported a study in which five groups of patients with Crohn's disease were treated with:-

- Group A - uncoated gelatine capsules containing 500 mg "Purepa" fish oil concentrate (containing EPA 40% and DHA 20%);
- Group B - gelatine capsule containing 500 mg "Purepa" fish oil concentrate and coated with a pH 5.5/120 minutes or cellulose acetate

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- trimellate ("CAT") coating;
- Group C - gelatine capsule containing 500 mg "Purepa" fish oil concentrate and coated with a pH 5.5/60 minutes CAT coating;
- 5 Group D - gelatine capsule containing 500 mg "Purepa" fish oil concentrate and coated with a pH 6.9/120 minutes cellulose acetate phthalate ("CAP") coating; and
- 10 Group E - uncoated gelatine capsule containing 1000 mg "Max-EPA" triglyceride fish oil (EPA 18% and DHA 10%).

15 CAP dissolves at pH 6.8 and CAT dissolves at pH 5.5. All the coated capsules disintegrate within 15 minutes at the relevant pH.

20 The four groups taking Capsule Types A to D took 9 capsules (2.7 g of omega-3 polyunsaturated acid) during meals 3 times daily for 6 weeks and those taking Type E capsules received 12 capsules (3.4 g of omega-3 polyunsaturated acid) daily in divided doses during meals over the 6 week period.

25 All of the five regimens increased the incorporation of the omega-3 polyunsaturated acid both in plasma and red blood cell phospholipid membranes by displacing arachidonic acid, linoleic acid, and to a lesser extent oleic acid. However, much more of the free omega-3 polyunsaturated fatty acid mixture was absorbed using the capsules

30 containing "Purepa" fish oil concentrate than when using "Max-EPA" triglyceride mixture. The incorporation was coating dependent and it is speculated to be related to the site of capsule-disintegration. The Group C capsules (having the pH 5.5/60 minutes coating) gave the best

35 incorporation of the omega-3 polyunsaturated fatty acids in the plasma and red blood cell phospholipid membranes. The

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Group D capsules (having the pH 6.9 coating) gave very poor incorporation and 70% of patients in this Group had increased daily bowel motion. Slightly better incorporation was registered with the Group B capsules (having the pH 5.5/120 minutes coating), but 50% of 5 patients in the Group reported diarrhoea.

The Group C capsules used by Belluzzi et al combined both pH and time-dependent release mechanisms and made it possible to avoid capsule-breakdown (pH 5.5) in the stomach-duodenum, and consequently void upper gastro-intestinal side-effects. Since they were only gastric resistant for 60 minutes, they allowed quick release of the fish oil concentrate in the small intestine and its complete absorption. 15

Surprisingly, it has now been found that the optimum combination of absorption and absence of side effects occurs if the release of polyunsaturated fatty acid is controlled to occur in the ileum, especially mid-ileum. 20

Thus, the present invention provides an oral dosage form, containing as an active principle an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof, which releases the acid in the ileum. 25

The present invention also provides the use of an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof in the manufacture of a medicament releasing the acid in the ileum for the treatment of inflammatory bowel disease. 30

Further, the present invention provides the use of said oral dosage forms in the treatment inflammatory bowel disease. 35

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It is preferred that the omega-3 polyunsaturated acid is DHA, EPA or a mixture thereof. It is present in free acid form or as a pharmaceutically acceptable salt thereof and can be present as the sole active principle or with
5 other active principles. Suitably, a fish oil concentrate containing at least 60% by weight DHA and EPA is used.

Omega-3 polyunsaturated acids are readily oxidised and hence an antioxidant usually will be present. The
10 presently preferred antioxidant is gamma-tocopherol but other pharmacologically acceptable antioxidants can be used, for example butylated hydroxy anisole, butylated hydroxy toluene, propyl gallate or a quinone.

15 The oral dosage form may also contain one or more pharmaceutically acceptable excipients depending upon the precise nature of the dosage form. Suitably, the oral dosage form can be a coated tablet containing the omega-3 polyunsaturated acid in a microencapsulated form or loaded
20 on a suitable absorbent. However, it is preferred that the oral dosage form is a coated capsule, especially a soft or, more especially, hard gelatine capsule.

The coating must be such as to release the acid in the
25 ileum, preferably in the mid-ileum. Usually, dissolution of the coating will be entirely time dependent but a coating relying on a combination of time and pH dependence can be used. Suitably, the coating is resistant for a period of 30 to 60 minutes at pH 5.5. The presently
30 preferred coating is a neutral polyacrylate such as a poly(ethylacrylate-methylmethacrylate), especially Eudragit NE 30-D (Röhm Pharma GmbH) which has an average molecular weight of about 800,000.

35 Usually, the omega-3 polyunsaturated acid will be administered in a daily dosage of 20 to 50 mg/kg,

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especially 30-40 mg/kg. The actual dose will vary depending inter alia on the identity of the omega-3 polyunsaturated acid and the nature and degree of the disorder being treated. Usually, each unit dose will
5 contain 250 to 1000 mg, especially 400 to 800 mg.

The following is a description, by way of example only, of a presently preferred embodiment of the invention.

10

Example 1

Transparent hard gelatine capsules (Elanco Qualicaps size 0; Lilly France SA) were each filled with 500 mg of a fish oil concentrate containing at least 60% by weight DHA and EPA (Incromega 3F60; Croda Universal Ltd, UK). The
15 filled gelatine capsules were film coated with Eudragit® NE 30-D to provide resistance for 30 to 60 minutes at pH 5.5 by spraying with a film coating composition (see below) at 35 ml/min using 0.8 bar pressure at 25°C and air drying for
20 at least 30 mins at 25°C.

The film coating composition (for 50,000 capsules) was prepared by slowly adding silicon anti-foam emulsion (0.36 mg), brown iron oxide (E 172; 3.00 mg), titanium dioxide
25 (2.35 mg) and talc (10 mg) in succession to water (75 mg) and agitating for 1 to 2 hours to form a very fine dispersion. A 30% aqueous dispersion of a poly(ethyl-acrylate-methylmethacrylate) having an average molecular weight of about 800,000 (Eudragit® NE 30D; 60 mg) and added
30 to polysorbate 80 (MO 55 F; 0.2 mg) in a little water and the resultant mixture agitated. Silicon anti-foam emulsion (2 or 3 drops) was added to destroy the resultant foam and the aforementioned dispersion was slowly added. The vessel was washed with water (25 mg) and the dispersion stirred
35 for 30 minutes before being filtered (150 µm).

Example 2

5 A double-blind placebo-controlled randomised study was conducted using 78 patients with well established diagnosis of Crohn's disease in clinical remission according to the Crohn's disease activity index (CDAI) and satisfying all the following criteria:-

- 10 (a) CDAI <150 for at least 3 months but less than 2 years;
- (b) at least one abnormal value of alpha-1 acid glycoprotein (>130 mg/dl), erythrocyte sedimentation rate (ESR);
- (c) (>40mm/h), or alpha-2 globulin (>0,9 g/dl);
- 15 (d) no treatment with 5-aminosalicylate, suiphasalazine or corticosteroids in the previous 3 months, or with immunosuppressive therapy in the previous 6 months;
- (e) no previous bowel resection >1 m; and
- 20 (f) age 18-75 years.

The patients were blindly randomised into two groups of 39 patients to receive daily either 9 enteric-coated hard gelatine capsules containing 500 mg of a fish oil concentrate ("Purepa"; see Table 1) or 9 enteric-coated capsules of identical appearance containing 500 mg of a placebo (Miglyol[®] 812). The fish oil concentrate contained 40% EPA and 20% DHA. Both sets of capsule were coated with Eudragit NE 30D to resist gastric acid or gut juice for at least 30 min and to disintegrate within 60 min at pH 5.5, allowing release of the fish oil in the small intestine. During the treatment the patients did not take any other medication. The clinical characteristics of both groups of patient are set forth in Table 2.

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Table 1

COMPOSITION OF CAPSULE CONTENTS

Lipid profile	Purepa (fish oil)	Miglyol (placebo)
	Free fatty acids %	Neutral oil
C 14:0	-	
C 16:0	0.4	
C 16:1	3.2	
C 16:2	2.1	
C 16:3	2.4	
C 16:4	5.2	
C 18:0	-	
C 18:1	0.8	
C 18:2	1.5	
C 18:3	1.3	
C 18:4	6.9	
C 20:1	-	
C 20:3	1.5	
C 20:4 (AA)	1.7	
C 20:5 (EPA)	42.4	
C 21:5	1.6	
C 22:5	0.5	
C 22:6 (DHA)	19.9	

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Table 2

CLINICAL CHARACTERISTICS OF PATIENTS

	PUREPA	PLACEBO
MALE	20	19
FEMALE	19	20
AGE (years; median (range))	34 (18-67)	39 (20-65)
SMOKERS	14/39	13/39
DURATION OF DISEASE (months, median (range))	68 (24-94)	66 (20-88)
PREVIOUS OPERATION < 1m	14/39	13/39
SITE OF INVOLVEMENT		
ileum	25	24
ileum + colon	14	15
CDAI median (range)	78 (28-120)	82 (30-112)
ESR (mm/h)	36.9 (SD 27-min 6;max 122)	35.7 (SD 24-min 12;max 90)
ALPHA-2 globulins (g/l)	9.6 (SD 1.8-min 6.1;max 13.2)	9.2 (SD 1.3-min 6.5;max 11.9)
ALPHA-1 GLYCOPROTEIN (mg/dl)	136.8 (SD 52-min 53;max 257)	137.1 (SD 58-min 60;max 263)

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Each patient in the fish oil group received 1.8 g of EPA and 0.9g of DHA daily for 12 months. They were examined on entry to the study and at 3, 6 and 12 months or before if symptoms worsened with an increase of CDAI of at least 100 points from baseline value and above 150 for more than 2 weeks. During each visit, laboratory tests were made of blood, kidney, liver, ESR, alpha-1 acid glycoprotein, alpha-2 globulin and CRP (c-AMP-Receptor-Protein). At time 0, 6 months and at the end of the study, 2 ml of packed red cells and polymorphonuclear leucocytes were obtained following the procedure described by Popp-Snijders et al (Scan. J. Clin. Lab. Invest 44 (1984) 39-46), and their membrane lipids were extracted as described by Dodge and Phillips (J. Lipid Res. 8 (1967) 667-675) using a 2:1 mixture of chloroform and methanol containing 0.01% butylated hydroxytoluene (2,6 di-tert-butyl-p-cresol) as antioxidant. Samples were stored under nitrogen at -20°C for less than 2 weeks prior to separation of the phospholipids and analysis of the omega-3 polyunsaturated fatty acids. Phospholipid fractions were obtained from the extracted lipids using 1-dimensional thin layer chromatography. The samples were spotted in one corner of a silica plate and developed with chloroform/methanol/acetic acid/water (25:14:4:2). The separated phospholipids were transmethyalted using 1 N potassium hydroxide in methanol and boron trifluoride in 14% methanol for 10 min at 80°C. Fatty acid methyl esters were then extracted in hexane, resuspended in 100 µl of benzene and analyzed by gas-chromatography equipped with a capillary column (0.32 mm i.d. x 25 m), using helium as the carrier gas (flow rate 3ml/min) and flame ionisation detection. The column temperature was programmed between 170°C and 210°C at 5°/min with the injector and detector temperatures at 220°C and 250°C, respectively. Individual fatty acid methyl esters were identified by comparison with commercial

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standards. Heptadecanoic acid (17:0) was used as the internal standard (1 mg/ml in benzene) and the results expressed as relative percentages.

5 The difference in the relapse rate in the fish oil and placebo groups was analyzed using the chi-squared test on a 'compliance only' and 'intention to treat' basis. Differences between features of patients in the active and the placebo group were analyzed using the Mann-Whitney U-
10 test, and the laboratory results were analyzed with Student's t-test for paired data (both tests 2-tailed). Kaplan-Maier life-table curves for patients remaining in remission were calculated according to the assigned treatment. Differences in the curves were tested by log
15 rank analysis. Multiple regression analysis was performed between some variables (trial treatment, gender, age, previous surgery, length of disease) and clinical relapses; the forward procedure was used for selecting a more representative model.

20 In the fish oil group, 1 patient withdrew (moved away) and 4 dropped out because of diarrhoea. In the placebo group, 1 patient withdrew (did not attend the outpatient clinic) and 1 dropped out because of diarrhoea. Diarrhoea
25 started in all 5 cases within the first month of treatment and symptoms did not improve when the daily capsule intake was reduced. This diarrhoea might have been due to the delivery of the capsule contents into the distal part of the gut. The coating is time-dependent (30-60 min at pH
30 5.5) so if the transit time is short, the capsules would remain intact further along the intestine.

 The relapse rate was significantly reduced by the fish oil compared to the placebo group: chi squared 11.75;
35 p=0.0004 (difference 41%, 95% confidence interval (CI) 16-

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66). This difference was significant too on an intention to treat analysis: chi squared 9.05; $p=0.0026$ (difference 32%, 95% (CI) 12-52).

5 Table 3 summarises the clinical results and Table 4
summarises the laboratory variables of inflammation at
entry and at 12 months in the patients who received the
fish oil and were still in remission at the end of the
study. No significant decrease in any of the laboratory
10 findings of disease activity occurred in the placebo group.
Table 5 shows the incorporation of the main fatty acids
into phospholipid membranes (AA = arachidonic acid and LA =
linoleic acid). Multiple regression analysis indicated
that only the fish oil capsules significantly affected
15 clinical relapse ($t=3,16$; $p=0,002$; F ratio=10; $p=0,002$).

Over a period of 12 months the fish oil capsules used
in the study reduced the clinical relapse of Crohn's
disease in comparison with placebo by 50%. It is important
20 to note that the patients in the study were in clinical
remission for less than 24 months prior to entry, and
presented laboratory evidence of inflammation. Patients of
this type have about 75% greater risk of relapse in
comparison with patients with long previous remission with
25 normal laboratory tests.

The results indicate that the fish oil capsules are
the most effective and safe available treatment for
preventing clinical relapses in Crohn's disease, with
30 relatively few side effects.

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Table 3

CLINICAL RESULTS AFTER 12 MONTHS OF TREATMENT

	fish oil (n=39)	placebo (n=39)
Withdrew	1	1
REMISSIONS	23/38	10/38
drop-out	4	1
RELAPSES (intention to treat) with drop out	15/38 (39,5%)*	28/38 (73,7%)
	*chi square 9.05; p = 0.0026	
excluding drop-outs	11/34 = 32,4%	27/37 = 73,0%
	*chi square 11,75; p = 0.0004	

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Table 4

23 PATIENTS GIVEN PUREPA IN REMISSION AFTER 12 MONTHS

	TIME 0	12 MONTHS
ESR (mm/h)	37.8(6-122)SD 25	19.5(3-40)SD 11.2
	p= 0.0002	
CRP (mg/dl)	3.6(0.2-9.9)SD 3.4	1.0(0.2-3.5)SD 0.9
	p= 0.001	
ALFA-2 GLOBULIN (G/DL)	0.91(0.64-1.32)SD 0.15	0.74(0.56-0.91)SD 0.1
	p= 0.001	
ALFA-1 GLYCOPROTEIN (mg/dl)	137(57-248)SD 49	111(69-180)SD 33
	p= 0.002	
ALBUMIN (g/dl)	3.7(3.0-4.4)SD 0.4	4.0(3.1-4.7)SD 0.35
	p= 0.004	
WBC	8780(4000-11700)SD 2093	7400(3310-11550)SD 2634
	p= 0.01	

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Table 5

PERCENTAGE OF MAIN FATTY ACIDS INCORPORATED INTO RBCs

	PUREPA		MIGLYOL	
	TIME 0	6 MONTHS	TIME 0	6 MONTHS
18:2n-6 LA	10.2±1	7.0±0.8	6.4±0.4	10.6±1.5
20:4n-6 AA	13.9±1.5	8.4±1.2	7.1±1.2	13.5±1.3
20:5n-3 EPA	0.2±0.1	4.1±0.3	5.8±0.6	0.3±0.1
22:6n-3 DHA	2.9±0.6	7.4±1.2	11.4±1.2	3.2±0.5

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CLAIMS

1. An oral dosage form containing as an active principle an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof, characterized in that it releases the acid in the ileum.
5
2. An oral dosage form as claimed in Claim 1, wherein the omega-3 polyunsaturated acid is released in the mid-ileum.
10
3. An oral dosage form as claimed in Claim 1 or Claim 2, wherein release of the omega-3 polyunsaturated acid is controlled by an exterior coating on a capsule containing the said active principle.
15
4. An oral dosage form as claimed in Claim 3, wherein delay in dissolution of the coating is time-dependant but not pH dependent.
- 20 5. An oral dosage form as claimed in Claim 4, wherein the coating is resistant for a period of 30 to 60 minutes at pH 5.5.
- 25 6. An oral dosage form as claimed in Claim 4 or Claim 5, wherein the coating is a neutral polyacrylate.
7. An oral dosage form as claimed in Claim 6, wherein the coating is a poly(ethylacrylate-methylmethacrylate).
- 30 8. An oral dosage form as claimed in any one of the preceding claims, wherein said acid is DHA, EPA or a mixture thereof.
- 35 9. An oral dosage form as claimed in any one of the preceding claims, wherein said acid is present as the sole active principle.

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10. The use of an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof in the manufacture of a medicament releasing the acid in the ileum for the treatment of inflammatory bowel disease.
- 5
11. A use as claimed in Claim 13, wherein the medicament is an oral dosage form as defined in any one of Claims 2 to 9.
- 10
12. The use of an oral dosage form as claimed in any one of Claims 1 to 9 in the treatment of inflammatory bowel disease.
- 15
13. A method of treating inflammatory bowel disease, which comprises administering to a patient an effective amount of an oral dosage form as claimed in any one of Claims 1 to 9.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/20 A61K9/48

International Application No
PCT/EP 96/02038

According to International Patent Classification (IPC) or to both national classification and IPC
B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 225 303 (AKO LAKEMEDEL) 10 June 1987 see page 2, line 40 - page 3, line 33	1-6,8-13
Y	GB,A,2 223 943 (TILLOTTS PHARMA) 25 April 1990 cited in the application see the whole document	1-6,8,9
Y	EP,A,0 289 204 (EFAMOL HOLDINGS PLC) 2 November 1988 cited in the application see claims 1,2,16 see page 4, line 4 - line 12 see page 4, line 29 - line 32 see page 9; example 4 -----	1-6,8-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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20 September 1996

Date of mailing of the international search report

03.10.96

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Ventura Amat, A

INTERNATIONAL SEARCH REPORT

In ternational application No.

PCT/EP 96/ 02038

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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